

Remarks

Claims 1-18 were pending in the subject application. Claims 1-5 and 8-14 remain pending but withdrawn from consideration. Accordingly, claims 6, 7, and 15-18 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Applicants acknowledge that claims 1-5 and 8-14 have been withdrawn from further consideration as being drawn to a non-elected invention. However, Applicants wish to reserve the right to request rejoinder of the non-elected process claims upon an indication of an allowable product claim in accordance with MPEP §821.04.

The application is objected to on the grounds that the subject specification fails to comply with the sequence requirements as set forth at 37 CFR 1.821 through 1.825. Specifically, the Examiner indicates that the specification contains sequences which do not include sequence identifiers. By this Amendment, the specification has been amended to provide sequence identifiers for each of the sequences in the application. A Submission of Sequence Listing and Statement under 37 CFR §§1.821-1.825, including a sequence listing on paper and computer readable format is attached. Reconsideration and withdrawal of the objection is respectfully requested.

Claims 6, 7, and 15-18 are rejected under 35 USC §103(a) as obvious over Bushman (WO 95/32225), Mannino *et al.* (1999), and Dujon *et al.* (U.S. Patent No. 5,474,896). The Bushman publication is cited as teaching chimeric proteins comprising a DNA binding domain and an integrase, wherein the DNA binding domain can be obtained from a restriction enzyme and wherein the integrase can be obtained from a retrovirus, including that of HIV-1. The Mannino *et al.* publication is cited as teaching the endonucleases PpoI and H98A and that they are specific to sites that are rarer in a genome. The Dujon *et al.* patent is cited as teaching the endonuclease CreI. Applicants respectfully traverse this ground of rejection.

Applicants respectfully assert that the cited references, taken alone or in combination, do not teach or suggest the claimed invention. The primary reference cited under this rejection, the Bushman publication, discloses the integration of viruses containing the integrase-LexA fusion protein. There is no natural genomic target for an integrase-LexA fusion protein. The binding sites are not unique in the human genome, meaning that LexA is not feasible for safe transgene

integration. Therefore, the Bushman publication merely describes the principle that the integrase molecule target site preference can be altered by fusing a targeting partner to an integrase.

The present invention is directed to solving a completely different problem, *i.e.*, the specific integration of a transgene comprising retrovirus-like nucleic acid into a eukaryotic genome. All natural DNA-binding proteins have their own DNA-binding site, and, therefore, present a natural genomic target. Accordingly, Applicants respectfully assert that the present invention is not obvious over the Bushman publication.

The secondary references do not cure the deficiencies of the Bushman publication. The Mannino *et al.* reference and Dujon *et al.* patent merely disclose particular endonucleases, and mention that they are specific to sites that are rarer in a genome. However, just because these endonucleases are more specific, does not mean that the skilled person would expect that they could be combined with the integrases disclosed in the Bushman publication, to accomplish site-specific integration. There is no suggestion in the Bushman publication that different DNA-binding domains should be investigated, or that site-specific integration could even be achieved. Therefore, Applicants respectfully assert that the present invention is not obvious over the reference cited by the Examiner.

As the Examiner is aware, in order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must generally find both the suggestion of the claimed invention, and a reasonable expectation of success in making that invention, solely in light of the teachings of the prior art and from the general knowledge in the art. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). One finds neither the suggestion, nor the reasonable expectation of success, of Applicants' claimed invention in the cited references and, therefore, the claimed invention is not obvious over the cited references. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Submission of Sequence Listing and Statement
Sequence Listing on paper and computer readable format